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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
GUSSOW, ANNE	
ART UNIT	PAPER NUMBER
1643	

NOTIFICATION DATE	DELIVERY MODE
12/08/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PATDOCTC@fr.com

Office Action Summary	Application No.	Applicant(s)	
	10/550,934	TSUCHIYA ET AL.	
	Examiner	Art Unit	
	Anne M. Gussow	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 September 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *15,16,19-22,28-31,36-39 and 44-83* is/are pending in the application.

4a) Of the above claim(s) *36-39 and 44-59* is/are withdrawn from consideration.

5)☒ Claim(s) *15,16 and 66-71* is/are allowed.

6)☒ Claim(s) *19-22,28-31,60-65 and 72-83* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/10/09, 10/28/09, 11/16/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Sequence alignment*.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on September 10, 2009 has been entered.

2. Claims 15, 16, and 19-22 have been amended.
Claims 1-14, 17, 18, 23-27, 32-35, and 40-43 have been cancelled.
Claims 60-83 have been added.

3. Claims 36-39 and 44-59 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on April 16, 2008.

4. Claims 15, 16, 19-22, 28-31, and 60-83 are under examination.

5. The following office action contains NEW GROUNDS of Rejection.

Information Disclosure Statement

6. The information disclosure statements (IDS) submitted on September 10, 2009, October 28, 2009, and November 16, 2009 are in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statements have been considered by the examiner and an initialed copy of the IDS is included with the mailing of this office action.

Rejections Withdrawn

7. The rejection of claims 17 and 18 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is withdrawn in view of applicant's cancellation of the claims.

8. The rejection of claims 14 and 23-27 under 35 U.S.C. 102(a) as being anticipated by Tedder is withdrawn in view of applicant's cancellation of the claims.

9. The rejection of claims 14 and 23-27 under 35 U.S.C. 102(a) as being anticipated by Tuscano, et al. is withdrawn in view of applicant's cancellation of the claims.

10. The rejection of claims 14 and 23-27 under 35 U.S.C. 102(e) as being anticipated by Tedder is withdrawn in view of applicant's cancellation of the claims.

11. The rejection of claims 14 and 23-27 under 35 U.S.C. 102(e) as being anticipated by Tuscano, et al. is withdrawn in view of applicant's cancellation of the claims.

Rejections Maintained/ NEW GROUNDS of Rejection

Claim Rejections - 35 USC § 112

12. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

13. The rejection of claims 20, 22, 29, 31, and newly added claims 60-65, 75-77, 81-83 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is maintained.

Applicant's arguments filed September 10, 2009 have been carefully considered by the examiner but they are deemed not to be persuasive. The response states that at the priority date of the instant application, it was well known in the art that the CDRs of an antibody are primarily responsible for antigen recognition. In addition, at the priority date, much progress had already been made in antibody engineering techniques to create better antibodies. The development of methods for the cloning and expression of antibody variable region gene sequences leading to the synthesis of functional antibody fragments, together with application of methods of random and site-directed mutagenesis, greatly facilitated structure- function studies of CDRs. Many different approaches had been reported for improving the affinity of antibodies, including error-prone PCR, CDR walking, and parsimonious mutagenesis, among others (see, references collected in Appendix A). The value of these methods is further enhanced by molecular modeling, allowing the prediction of suitable amino acids for substitution in CDRs. The use of these techniques combined, in some instances, with powerful phage display technology (see, Appendix A, Marks et al., J. Biol. Chem., 267:16007 (1992))

has permitted the routine production of variant antibodies with improved affinity well before the priority date of the instant application (see, Appendix A, Cumbers et al., Nat. Biotechnol., 20:1129-1134 (2002); Schier et al., J. Mol. Biol., 263(4):551-67 (1996); Yang et al., J. Mol. Biol., 254(3):392- 403 (1995); Deng et al., J. Biol. Chem., 269:9533 (1994); Barbas et al., Proc. Natl. Acad. Sci. USA, 91:3809 (1994); Sharon, Proc. Natl. Acad. Sci. USA, 87:4814 (1990); and Roberts, Nature, 328:731 (1987)). These references clearly demonstrate the level of knowledge in the antibody engineering field and the significant maturity of this field at the priority date of this application (see response pages 8-11).

In response to this argument, while the examiner agrees that the CDR regions of the antibody are essential for antigen binding it is well known in the art that even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff, et al. (Proceedings of the National Academy of Sciences, 1982. Vol 79, page 1979, as cited on the PTO-892 mailed June 12, 2008). Rudikoff, et al. teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function.

MacCallum, et al. (Journal of Molecular Biology, 1996. Vol. 262, pages 732-745, as cited on the PTO-892 mailed June 12, 2008) analyzed many different antibodies for interactions with antigen and state that although CDR3 of the heavy and light chain dominate, a number of residues outside the standard CDR definitions make antigen contacts (see page 733, right column) and non-contacting residues within the CDRs

coincide with residues as important in defining canonical backbone conformations (see page 735, left column). De Pascalis, et al. (Journal of Immunology, 2002. Vol. 169, pages 3076-3084, as cited on the PTO-892 mailed June 12, 2008) demonstrate that grafting of the CDRs into a human framework was performed by grafting CDR residues and maintaining framework residues that were deemed essential for preserving the structural integrity of the antigen binding site (see page 3079, right column). Although abbreviated CDR residues were used in the constructs, some residues in all 6 CDRs were used for the constructs (see page 3080, left column).

The fact that not just one CDR is essential for antigen binding or maintaining the conformation of the antigen binding site is underscored by Casset, et al. (Biochemical and Biophysical Research Communication, 2003. Vol. 307, pages 198-205, as cited on the PTO-892 mailed June 12, 2008) which constructed a peptide mimetic of an anti-CD4 monoclonal antibody binding site by rational design and the peptide was designed with 27 residues formed by residues from 5 CDRs (see entire document). Casset, et al. also states that although CDR H3 is at the center of most if not all antigen interactions, clearly other CDRs play an important role in the recognition process (page 199, left column) and this is demonstrated in this work by using all CDRs except L2 and additionally using a framework residue located just before the H3 (see page 202, left column). Vajdos, et al. (Journal of Molecular Biology, 2002 Vol. 320, pages 415-428, as cited on the PTO-892 mailed June 12, 2008) additionally state that antigen binding is primarily mediated by the CDRs more highly conserved framework segments which connect the CDRs are mainly involved in supporting the CDR loop conformations and in

some cases framework residues also contact antigen (page 416, left column). Holm, et al. (Molecular Immunology, 2007. Vol. 44, pages 1075-1084, as cited on the PTO-892 mailed June 12, 2008) describes the mapping of an anti-cytokeratin antibody where although residues in the CDR3 of the heavy chain were involved in antigen binding unexpectedly a residue in CDR2 of the light chain was also involved (abstract). Chen, et al. (Journal of Molecular Biology, 1999. Vol. 293, pages 865-881, as cited on the PTO-892 mailed June 12, 2008) describe high affinity variant antibodies binding to VEGF wherein the results show that the antigen binding site is almost entirely composed of residues from heavy chain CDRs, CDR-H1, H2, H3 (page 866). Wu, et al. (Journal of Molecular Biology, 1999. Vol. 294, pages 151-162, as cited on the PTO-892 mailed June 12, 2008) state that it is difficult to predict which framework residues serve a critical role in maintaining affinity and specificity due in part to the large conformational change in antibodies that accompany antigen binding (page 152 left column) but certain residues have been identified as important for maintaining conformation.

Each of these references speaks to the importance of the amino acid residues not only in the CDR regions but also in the framework regions of the antibodies. The instant specification as filed has not described which amino acid residues in either the CDR regions or the framework regions are essential for antigen binding. Applicant has not described which amino acid residue positions can be substituted and retain antigen binding.

Therefore after a fresh consideration of the claims and the evidence provided the rejection is maintained.

Claim Rejections - 35 USC § 103

14. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

15. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

16. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

17. Claims 19, 20, 28, 29, 60-62, and 72-77 are rejected under 35 U.S.C. 103(a) as being unpatentable over Leung, et al. (US PAT 5,789,554, issued August 4, 1998, as cited on the IDS filed September 10, 2009) in view of Tedder (US PG PUB 2003/0202975, published October 30, 2003, as cited on the PTO-892 mailed March 16, 2009).

The claims recite a diabody that recognizes CD22, wherein the diabody (a) comprises the amino acid sequences of complementarity determining regions (CDRs) 1-3 from SEQ ID NO: 5 and the amino acid sequences of CDRs 1-3 from SEQ ID NO: 7, and (b) induces apoptosis of a tumor cell expressing CD22, wherein the diabody is humanized, wherein the diabody induces lymphoma or leukemia cell apoptosis, wherein the diabody is a dimer of two scFv, held together by non-covalent bonds, wherein the diabody is a single chain diabody. A diabody that recognizes CD22, wherein the diabody comprises (a) the amino acid sequences of CDRs 1-3 from SEQ ID NO: 5 in which 0-3 amino acids in each of the CDRs of SEQ ID NO: 5 are substituted with another amino acid and (b) the amino acid sequences of CDRs 1-3 from SEQ ID NO: 7 in which 0-3 amino acids in each of the CDRs of SEQ ID NO: 7 are substituted with another amino acid and wherein the diabody induces apoptosis of a tumor cell expressing CD22, wherein the diabody is humanized, wherein each of the substituted amino acids is a conservative amino acid substitution, wherein no more than one amino acid is substituted in each CDR, wherein each substituted amino acid is a conservative amino acid substitution, wherein the diabody induces lymphoma or leukemia cell

apoptosis, wherein the diabody is a dimer of two scFv, held together by non-covalent bonds, wherein the diabody is a single chain diabody.

Leung, et al. teach an LL2 antibody that is specific for B-cell lymphoma and lymphocytic leukemia that comprises sequences which are identical to the instant SEQ ID Nos. 5 and 7 (thus comprising the CDR regions of SEQ ID Nos. 5 and 7, see sequence alignment). Leung, et al. do not teach a diabody. This deficiency is made up for in the teachings of Tedder.

Tedder teaches a diabody that binds CD22 with pro-apoptotic properties for the treatment of leukemia (paragraph 4). Tedder teaches the diabody may be chimeric, humanized, primatized, or human (paragraphs 26-27). Tedder teaches diabodies comprise a heavy chain variable domain connected to a light chain variable domain with a short linker (thus a single chain, see paragraphs 60-61).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced a diabody comprising the sequences of Leung, et al. and the diabody structure of Tedder.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced a diabody comprising the sequences of Leung, et al. and the diabody structure of Tedder because Tedder teaches antibodies that bind to CD22 for the treatment of leukemia. Further, Leung, et al. teach antibodies that bind to B-cells and comprise the identical sequence to the instant SEQ ID Nos. 5 and 7. Since the claims recite that the antibody of SEQ ID Nos. 5 and 7 binds to CD22, the antibody of Leung, et al. would necessarily bind to CD22

because it is the identical sequence. Therefore, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have used the antibody sequence of Leung, et al. in the diabody of Tedder because both antibodies bind to the same antigen for the same purpose. Additionally, since Leung, et al. and Tedder teach antibodies that bind CD22, and the instant claims comprise antibodies that bind CD22 to be useful for the same purpose, the claims are subject to an In re Kerkhoven analysis (In re Kerkhoven, 626, F.2s 846, 850, 205 USPQ 1069, 1072 (CCPA 1980)). The court held that it is obvious to combine two compositions, in order to form a third composition, when each of the two compositions is taught by the prior art to be useful for the same purpose. The idea of combining them flows logically from their having been individually taught in the prior art (MPEP 2144.06). Thus, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to have used sequences of Leung, et al. and produce a diabody in view of Tedder.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

18. Claims 21, 22, 30, 31, 63-65, and 78-83 are rejected under 35 U.S.C. 103(a) as being unpatentable over Leung, et al. (WO 2003/002607, published January 9, 2003) in view of Tedder (US PG PUB 2003/0202975, published October 30, 2003, as cited on the PTO-892 mailed March 16, 2009).

The claims recite a diabody that recognizes CD22, wherein the diabody (a) comprises the amino acid sequences of CDRs 1-3 from SEQ ID NO: 9 and the amino acid sequences from CDRs 1-3 in SEQ ID NO: 11, and (b) induces apoptosis of a tumor cell expressing CD22, wherein the diabody is humanized, wherein the diabody induces lymphoma or leukemia cell apoptosis, wherein the diabody is a dimer of two scFv, held together by non-covalent bonds, wherein the diabody is a single chain diabody. A diabody that recognizes CD22, wherein the diabody comprises (a) the amino acid sequences of CDRs 1-3 from SEQ ID NO: 9 in which 0-3 amino acids in each of the CDRs of SEQ ID NO: 9 are substituted with another amino acid; and (b) the amino acid sequences of CDRs 1-3 from SEQ ID NO: 11 in which 0-3 amino acids in each of the CDRs of SEQ ID NO: 11 are substituted with another amino acid; and wherein the diabody induces apoptosis of a tumor cell expressing CD22, wherein the diabody is humanized, wherein each of the substituted amino acids is a conservative amino acid substitution, wherein no more than one amino acid is substituted in each CDR, wherein each substituted amino acid is a conservative amino acid substitution, wherein the diabody induces lymphoma or leukemia cell apoptosis, wherein the diabody is a dimer of two scFv, held together by non-covalent bonds, wherein the diabody is a single chain diabody.

Leung, et al. teach an antibody that comprises amino acid sequences which are 99.5% identical to SEQ ID No. 11 (one amino acid substitution difference) and 100% identical to SEQ ID No. 9 (see sequence alignment). Leung, et al. do not teach a diabody. This deficiency is made up for in the teachings of Tedder.

Tedder has been described supra.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced a diabody comprising the sequences of Leung, et al. and the diabody structure of Tedder.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced a diabody comprising the sequences of Leung, et al. and the diabody structure of Tedder because

Tedder teaches antibodies that bind to CD22 for the treatment of leukemia. Further, Leung, et al. teach antibodies that bind to B-cells and comprise the identical sequence to the instant SEQ ID No. 9 and a sequence with a single substitution different from SEQ ID No. 11 (99.5% identical) which would comprise the identical CDRs of SEQ ID Nos. 9 and 11 as required by claims 21 and 22. Since the claims recite that the antibody of SEQ ID Nos. 9 and 11 binds to CD22, the antibody of Leung, et al. would necessarily bind to CD22 because it is the identical sequence. Therefore, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have used the antibody sequence of Leung, et al. in the diabody of Tedder because both antibodies bind to the same antigen for the same purpose. Additionally, since Leung, et al. and Tedder teach antibodies that bind CD22, and the instant claims comprise antibodies that bind CD22 to be useful for the same purpose, the claims are subject to an In re Kerkhoven analysis (In re Kerkhoven, 626, F.2s 846, 850, 205 USPQ 1069, 1072 (CCPA 1980)). The court held that it is obvious to combine two compositions, in order to form a third composition, when each of the two

compositions is taught by the prior art to be useful for the same purpose. The idea of combining them flows logically from their having been individually taught in the prior art (MPEP 2144.06). Thus, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to have used sequences of Leung, et al. and produce a diabody in view of Tedder.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Conclusion

19. Claims 15, 16, and 66-71 appear to be in condition for allowance.

Claims 19-22, 28-31, 60-65, and 72-83 are rejected.

20. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Leung, et al. US PG PUB 2003/0103979, published June 5, 2003, filed November 16, 2001. Leung, et al. teach chimeric LL2 antibodies for the treatment of leukemia.

Saxe. WO 97/34632, published September 25, 1997. Saxe, et al. teach a humanzied monoclonal antibody specific for B-cells.

21. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne M. Gussow whose telephone number is (571)272-6047. The examiner can normally be reached on Monday - Friday 8:30 am - 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Anne M. Gussow
December 3, 2009

/Anne M. Gussow/
Examiner, Art Unit 1643